

BIO MAGNETISM '87

6th International Conference on Biomagnetism
Tokyo, Japan August 27–30, 1987

Edited by

K. Atsumi

M. Kotani

S. Ueno

T. Katila

S. J. Williamson



Tokyo Denki University Press

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PREFACE

The 6th International Conference on Biomagnetism which was held from August 27, 1987, to August 30 at the Sankei Kaikan in Ohtemachi, Tokyo was a success with about 300 participants from 22 countries attending.

In this conference: the research of biomagnetism (mainly magnetoencephalograph (MEG), magnetocardiograph and magnetopneumograph), the SQUID (Superconducting Quantum Interference Device) technology to detect biomagnetism and other related topics were discussed.

The first conference was held in a free-discussion style in 1976 in Boston and the second one was in 1978 in Grenoble. The third conference was held in 1980 in Berlin where the style was changed to the formal presenting of papers. The fourth conference was in 1982 in Rome and the fifth in 1984 in Vancouver.

Although the first three conferences were small-scale workshops under the LT (Low Temperature) International Conference, at the fourth conference, it became independent. At that time, most of the participants were scientists and engineers. The 6th conference, however, was attended not only by those who are engaged in biomagnetism, but also by people in basic medicine and the clinical medicine world. This seems to suggest that biomagnetism has come to a turning point, from basic to clinical applications.

173 papers including 161 general subjects, 12 special subjects, and invited lectures were read in this conference. Furthermore, 4 round-table discussions were held. Compared to the 59 theses at Rome Conference and the 70 at Vancouver, the Tokyo Conference presented two or three times as many. The general subjects were basically as follows; 67 on magnetoencephalography and neuromagnetism, 26 on magnetocardiography and cardiomagnetism, 19 on the SQUID and 17 on the magnetopneumograph. These accounted for 70% of the total. Among the others were 23 on the bioaction of magnetism, 4 on MRI (Magnetic Resonance Imaging), 3 on magnetic bacteria and biomagnetic particles, and 2 on the magnetomusculargraph and dermatomagnetism.

In this conference, most of the papers were on neuromagnetism. Theses on neuromagnetism were further classified into the followings: 18 on a model for magnetoencephalograph and the inverse problem, 15 on the spontaneous magnetocardiograph such as alpha-rhythm, 11 on the auditory evoked response, 15 on the visual evoked response, 6 on the corporeal evoked response, 5 on the epilepsy magnetocardiograph, 3 on the measurements of the magnetic field in the cerebellum in vitro or hippocampal slices, and two on ophthalmography.

Regarding the auditory evoked response, both the joint team of Berlin and Munster and the research team of Densoken reported that for the first time they succeeded in the detection of the magnetic field from the brainstem. That is, they finally detected the magnetic field corresponding to the auditory brainstem responses (ABR) which had previously been extremely difficult to measure. Since the ABR micromagnetic field is on the order of $5 \cdot 10^{-11}$ T (10 T), it is the smallest existing biomagnetic field to be measured. This measurement will be more and more important to judge cerebral death or understand the functions of the brainstem.

In the round-table discussion of MEG on the first day and the epilepsy discussion on the second day, comments were made regarding the contribution of the research of neuromagnetism toward the clarification of brain functions and the usefulness of MEG to diagnose causes of focal epilepsy. Through this conference, it can be hoped that the research of neuromagnetism will promote the development of the multi-channel SQUID system and will finally lead to the realization of the imaging NMI (Neuro Magnetic Imaging) of brain functions.

As for cardiomagnetism, it was discussed in a round table session whether heart disease which cannot be detected by electrocardiogram can be detected by a magnetocardiogram, and also what kind of heart disease the magnetic field measurement is effective in diagnosing. In both the invited and general lectures, the idea that the magnetocardiograph is useful for the diagnosis of myocardial ischemia was introduced. Also, the measurement of local micro-cardiomagnetism as being effective for the diagnosis of WPW (Wolff-Parkinson-White) syndrome was mentioned.

Regarding the magnetopneumonicgraph, it was proved that the cytoplasmic motility of alveolar macrophages is important for relaxation and that the magnetopneumonicgraph is effective for monitoring dust accumulation in lungs and the diagnosis of silicosis.

In the round-table discussion on the SQUID, a trial SQUID system which works in nitrogen temperature was introduced with the use of high-temperature super conducting materials. Also, interesting results regarding biomagnetism were given out.

These proceedings contain theses carefully selected among those which were written and used in the conference. Although according to the initial schedule the proceedings were to be issued in December, 1987, it took an unexpectedly long time to read all the theses and publishing was delayed until now.

We, the editors, would like to express sincere appreciation to everybody for their cooperation and support toward the success of the Tokyo Conference and the publishing of the proceeding.

We are sure that this book will contribute to the development of the research of biomagnetism in the future.

K. Atsumi

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K. Atsumi M. Kotani
S. Ueno T. Katila
and
S. J. Williamson

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Date

August 27 (Thu.) – 30 (Sun.), 1987

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Cooperation

Japan Society of Medical Electronics and Biological Engineering
The Institute of Electrical Engineers of Japan
The Magnetics Society of Japan
The Japanese Society of Electrocardiology
Japan Society of Electroencephalography and Electromyography
Japan Society of Chest Disease
The Japanese Circulation Society
Japan Neurosurgical Society
Japanese Society of Neurology
Cryogenic Association of Japan
The Japanese Association for Thoracic Surgery
The Japan Society of Applied Physics
The Institute of Electronics and Communication Engineers of Japan

Official Language

The official language of the Conference is English.

TIME SCHEDULE

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	Morning					Afternoon			Evening
27 Thu.	9:00 9:30 10:00 11:00 11:15 ... 12:15					13:30 16:00 16:15 17:45			
	Opening Ceremony	Cohen	Williamson Katila	Session MEG Model (4)		Session Evoked Responses (10)	Round Table MEG		
28 Fri.	8:30 10:00 10:15 12:30					13:30...14:00 16:00 16:15 17:45			
	Hari Narici Kuriki		Session Neuromagnetism I (9)			Roth Session Neuromagnetism II (8)	Round Table Epilepsy		
29 Sat.	8:30 10:00 10:15 11:45 11:50 12:30					13:30 16:15 16:30 18:15			Banquet (Hotel Grand Palace)
	Schmitz Stroink Mori	Round Table MCG		Business Meeting		Session MCG (11)	Session MCG Model (7)		
30 Sun.	8:30 9:30 9:45 12:00					13:00 14:30 14:45 15:00			
	Brain Takishima		Session Lung and Relaxation (9)			Round Table SQUID	Closing Ceremony		

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	Morning		Afternoon		Evening
27 Thu.	11:15 12:30		13:30 15:45		Wel- coming Recep- tion
	Session Related Topics (5)		Session Effects (9)		
28 Fri.	10:15 12:30		14:00 15:15		
	Session SQUID & Device I (9)		Session SQUID & Device II (5)		
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30 Sun.					

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INTRODUCTION:
AN OVERVIEW OF BIOMAGNETISM IN 1987

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INTRODUCTION

A scientist visiting our lab pointed out that biomagnetism in 1987 was like a new fruit tree. It had earlier produced its colored blossoms which are now gone, and everyone is waiting to see what fruit this tree will produce. The blossoms were the early discoveries that human organs, such as the heart and brain, produced magnetic fields which could be measured. The tree is now in a development stage, and it is certainly working hard to produce its fruit. Further, it is being watered by considerable money. But what will this fruit be? Will it consist of widespread use of MEGs in hospitals? Will it be the common use of lung detectors in occupational medicine? Or will it be something unforeseen?

In this talk I'll try to give an overview of this tree. First, for the newcomers, I'll repeat the definition of biomagnetism, to show what type of tree this is. I won't give a history of biomagnetism because this has been done several times before (1,2), but at least I will say a little about the history of these conferences. Then I'll say something about the status of biomagnetism today. To show growth, I'll compare this 1987 conference with previous conferences. Then, I'll discuss several new technical developments that could strongly affect biomagnetism. Next I'll consider a major technical problem today, and some basic ideas that address these problems. Finally, I will review guesses by different people about the future of biomagnetism, that is, about the fruit of this tree.

DEFINITION OF BIOMAGNETISM

Most of us continue to use this definition: "Biomagnetism is the phenomenon where biological material produces an external magnetic field." We note that biological material produces an external magnetic field in three ways. First, it can produce a field in a natural way; muscles or nerves naturally generate electrical ion currents in the body, and these currents produce the external field. Examples of these are the currents generated by the heart muscle or by the brain; these produce a magnetic field over the chest (the magnetocardiogram or MCG), or a magnetic field around the head (the magnetoencephalogram or MEG). In the second way, biological material can produce a magnetic field due to iron-like particles within the material, usually Fe_3O_4 . These are usually contaminating particles which enter the body in various ways, such as being inhaled into the lung. These produce a remanent magnetic field after they have been aligned by an applied magnetic field which is then removed. These particles can also be produced naturally in the biological material, as in some bacteria and in chitons and other creatures. In the third way, biological material itself (without particles) can produce a magnetic field in response to an applied field; this induced field exists only during the time the applied

field is maintained, and is related to the susceptibility of the tissue. This conference mostly involves the first two ways.

Therefore, we can think of our tree as consisting of three main branches: biomagnetism due to currents, due to iron-like particles, and biomagnetism related to susceptibility.

We again note that this definition of biomagnetism does not include the effects of an external magnetic field on living biological material. That is another phenomenon, not directly related to our definition, and is often called magnetobiology. Nevertheless, various members of the biomagnetic community, especially in Japan, maintain an interest in this phenomenon, and quite a few magnetobiology and papers of this type are presented here. Perhaps we can think of magnetobiology as a nearby, friendly tree.

HISTORY OF THESE CONFERENCES

The first conference was held in Cambridge (USA) in 1976. Thereafter, they were held mostly at two-year intervals. The 1978 conference was held in Grenoble (France), the 1980 conference in Berlin (Germany), the 1982 conference in Rome (Italy), and the 1984 in Vancouver (Canada). In addition, There were two related conferences: The first was a NATO Advanced Study Institute held in Frascati (Italy) just before the Rome conference, and the other was a conference in medical and biological engineering, held in Espoo (Finland) in 1985, where biomagnetism was strongly represented. The three-year gap between the Vancouver and Tokyo conferences was meant to accomodate this Finland conference. Proceedings have been published beginning with the 1980 conference and onward, including NATO and Finland. At the first conference in 1976 there were 22 official attendees, while here in Tokyo there are about 300, so that is one indication of how we have grown considerably during these eleven years. As a further indication, the number of countries represented at the first conference was five, while here in Tokyo that number is 21. Also, for the first time, we have parallel sessions because of the large number of presentations.

PRESENT STATUS OF BIOMAGNETISM

Table I represents a guess as to the extent of biomagnetism around the world. The first row indicates the separate places where biomagnetism is studied. In the next row, the number of professional researchers is meant to include those doing biomagnetic research part-time, and includes graduate students. Then we see the estimate of refereed papers each year; this has now increased to the point where one can't seriously read them all, or even those in neuromagnetism. Finally, the number of active funding awards is especially a vague guess, partly because the system of funding varies so greatly from country to country.

TABLE I. Extent of Biomagnetism in 1987

Groups or separate projects around the world	50 to 70
Professional researchers (incl. grad. students)	200 to 300
Refereed papers each year (incl. biomagn. conf.)	150 to 200
Active funding awards	70 to 90

Table II is a different and better quantitative indication of what is happening today. We can see the trends in biomagnetism by comparing the papers presented here in Tokyo with those of the past two biomagnetic conferences. By far the largest increase is in neuromagnetism, where the number of papers has more than

TABLE II. Change in Number of Conference Papers

<u>Subdivision</u>	<u>Rome(1982)</u>	<u>Vancouver(1984)</u>	<u>Tokyo(1987)</u>
Instrumentation	10	13	18
Neuromagnetism (incl.theory)	15	25	60
Cardiomagnetism (incl.theory)	13	15	24
Lung and relax. in cells	3	13	19
Other biomagnetism	<u>5</u>	<u>1</u>	<u>13</u>
Total biomagnetism	46	67	134
Related subjects	<u>2</u>	<u>2</u>	<u>30</u>
Total of all	48	69	164

doubled since the Vancouver conference. The other areas have increased substantially as well, but not quite so rapidly. There is only a diffuse boundary between lung biomagnetism (pneumomagnetism) and relaxation in cells (cytomagnetism), so they are grouped together. "Other biomagnetism" refers to other organs such as skeletal muscle, or general biomagnetic theory. Related subjects indicates magnetobiology and several other studies.

It is in neuromagnetism that we will see a special trend, as we study the papers presented here; it is a change in the equipment used. What we will see is the proliferation of multi-channel SQUID systems and magnetically shielded rooms. In a sense, this is the key feature of this Tokyo conference. Because it is time-consuming to map brain signals over the head with single-channel SQUID system, it has become simply necessary for MEG labs to use multi-channel SQUID systems. Further, because the brain signals are so weak, it has become necessary to improve signal/noise by investing in a shielded room. Thus, in the world today, one guesses that there are perhaps fifteen or twenty multi-channel systems of various types being built or already used, with almost as many shielded rooms, also of various types.

It is also in neuromagnetism that some of the largest groups are involved. Certainly the largest assembly is in New York City, where there are three affiliated groups at NYU (campus and medical school), one under the leadership of Profs. Samuel Williamson and Lloyd Kaufman, another under them and Profs. Llinas and Nicholson, and a third under Prof. Okada. They operate the superb Gemini, the largest SQUID system in the world, shown in Fig. 1. Perhaps the next largest assemblies are those in Helsinki and Rome. In Helsinki there are two groups, one affiliated with Prof. Lounasmaa and Dr. Hari, and the other with Prof. Katila. In Rome, the assembly is lead by Prof. Romani, Dr. Carrelli, and others. Another group in neuromagnetism, new and growing, is at the Los Alamos National Lab (New Mexico), under Dr. Edward Flynn. In other areas of biomagnetism there is a growing assembly in Tokyo (where Prof. Kotani is the main leader), and in Moscow as well.

We should note that large is not necessarily best, and some fine contributions in biomagnetism can come from a small project. I here mention one case of this type in the Boston area. This is the contribution by Dr. Peter Valberg at the Harvard School of Public Health. What Dr. Valberg has done, in a beautiful series of experiment (3), is verify without doubt that the relaxation phenomenon in lungs was due to cytoplasmic motion within macrophage cells. Working quietly, without fanfare, he has proceeded in proving what relaxation is all about, and I believe has set the groundwork for far-reaching future studies. Of course there is much fine work by other single investigators, and my apologies for not being able to list them all.

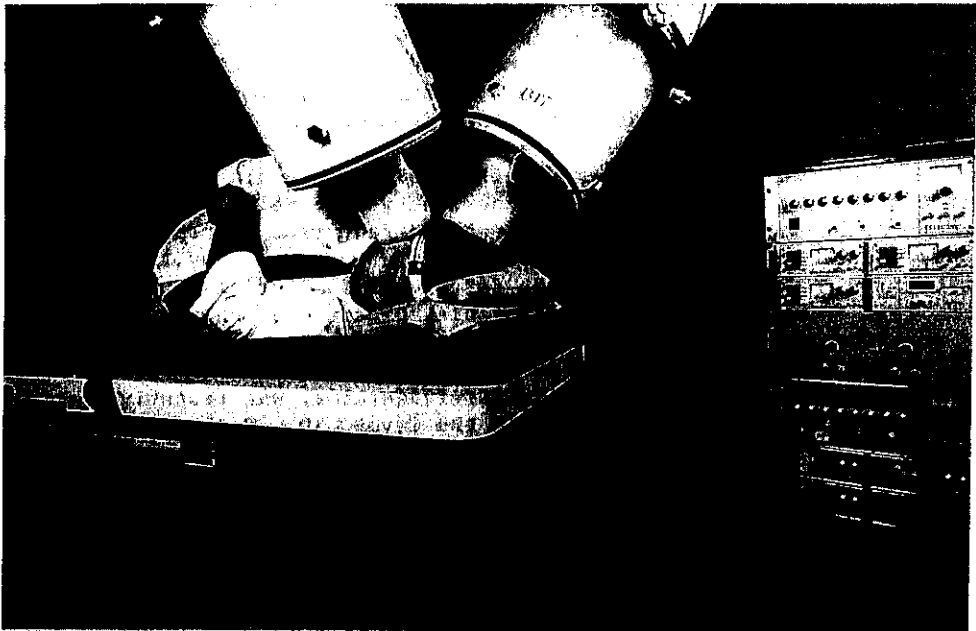


Fig.1. The Gemini system at the NYU Center for Neuromagnetism at Bellevue Hospital. It consists of two dewars, each containing seven dc SQUID channels, and is located in a two-shell magnetically shielded room. This system indicates the present trend in neuromagnetism: multi-channel MEG sensors used in a shielded room. The system and much of the technology was designed and built by BTi, and represents some of their most elaborate MEG equipment.

TWO RECENT NEW DEVELOPMENTS

There have been two developments, very new, which could have a strong impact on the future of biomagnetism. The first, we know, is the recent discovery of high-temperature superconductivity, and the second is the actual operation of a SQUID in a closed-cycle refrigerator. Concerning the high-T superconductor, I have asked some experts how this will affect SQUID measurements of weak magnetic fields, in particular when SQUIDS will operate in liquid nitrogen, now almost accomplished. They all agree that the fundamental low-noise limit goes up with some power of the temperature, perhaps the first power. In that case, the fundamental noise in going from liquid helium to liquid nitrogen would increase by a factor of 20. Now this doesn't look too promising for biomagnetism, especially brain measurements, but then Dr. William Black of BTi pointed out that it is not as simple as that. Presently, he said, the best sensitivity in a commercial SQUID is about $5\text{fT}/\sqrt{\text{Hz}}$, and this is not a thermal limit but is called "system noise", which includes the noise of the rf shield, and perhaps some electronics. Such noise would perhaps not go up as fast with temperature as noise in the SQUID. So, at best, complete system noise at liquid-nitrogen temperature possibly could be as low as $20\text{fT}/\sqrt{\text{Hz}}$.

Such noise would be acceptable in cardiomagnetism, and certainly in pneumomagnetism. In cardiomagnetism, hospital and clinic use could become convenient, perhaps for some screening purpose. In pneumomagnetism, it would become simple to measure very small amounts of magnetic contaminants in the lung, say in routine occupational measurement. In neuromagnetism, this number of 20 doesn't

look too good, especially if we begin to use high-order pick-up coils which are less efficient. Dr. Black therefore says, "The low-noise MEG will be a liquid helium technology for some time to come." However, he notes that high-T superconductivity can make at least one contribution to the MEG: It will allow the pick-up coil to be moved into the dewar vacuum space, closer to the head. A high-T coil would not introduce noise, and need only be superconducting.

One other application of high-temp superconductivity could be in the area of magnetic shielding. We know that the perfectly shielded room would be a closed superconducting shell, therefore an almost perfect room (except for holes) could be made, where the walls are cooled with liquid nitrogen, say. However, if one works out the cost of this room, even for higher-T materials, the present high- μ type of room is much more favorable. Therefore, unless there appears a magic room-temp. superconductor, the shielding application is not promising.

The other development, the closed-cycle refrigerator, was recently announced by BTI and the NYU group (4); it is called the CryoSQUID. We have heard the basic idea at previous conferences, but now it does appear to be working. In brief review, the SQUID is here cooled by a closed-cycle gaseous helium refrigerator, so that it doesn't need periodic refilling with liquid helium, hence doesn't need a large reservoir in the dewar. Therefore, the SQUID can become as simple to operate as a home refrigerator (but much more expensive!). Although the NYU system can apparently measure the brain activity, it relies on a computer to subtract noise in the signal due to the moving parts. Nevertheless, it appears that BTI is close to commercial production of such a system, and if the cost were manageable, this could popularize biomagnetism.

A PROBLEM IN BIOMAGNETISM AND SOME IDEAS

In the spirit of an overview, we will consider here what is perhaps the central problem in neuromagnetism in 1987; because neuromagnetism is the largest branch of biomagnetism, this then becomes a central problem in biomagnetism as a whole. However, before stating the problem, let's understand how the MEG is viewed by the neuroscience and neurology community. In that community, the MEG is evaluated against the EEG; it does not stand by itself. If it is to be needed and accepted by that community, then the MEG must give information about the brain sources which is considerably different or better than given by the EEG. This directly involves the number of channels. The more channels in the EEG or MEG, the more the information about the sources, up to some limit; for the clinical EEG the norm these days is 16 channels, while for the research EEG it can be many more. The MEG is evaluated against this kind of number. We can now state the problem: How can we get at least 16 channels of MEG, where each channel is just as effective, in its own way, as an EEG channel?

One solution, we know, is to try to get 16 or more channels into one large dewar which fits over the head. However, the trouble here is that a large dewar doesn't fit well to the head, and where its surface doesn't touch the scalp the pickup coils are far from the grain. Calculations show that the information content of the brain's magnetic field drops off as we increase the distance from the scalp; the magnetic lines are not straight lines like a radiation source--they bend and blend. With a planar gradiometer, the information drops off quite rapidly, and one centimeter makes quite a difference. Therefore, if and when there are 16 channels in one dewar, each channel would not be as effective as we would like, and this applies as well to spreading the channels between two dewars, now possible. Large dewars of this type would be good, but perhaps not good enough.

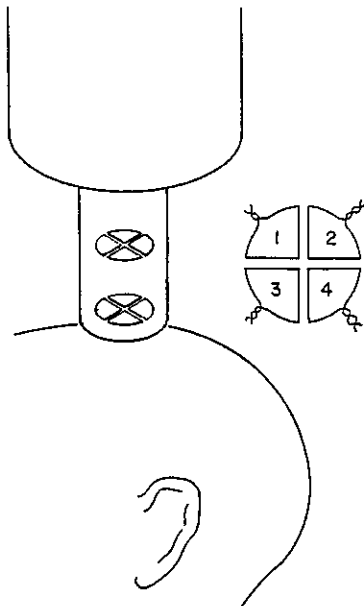


Fig. 2. An MEG system which may be possible, where many channels of information are obtained from one dewar at only one location. The tail of the dewar here contains two coil structures, where each has four quadrants, showed at the right. Each coil feeds a SQUID. When the SQUID outputs are combined in various ways, this system will yield B_z and various combinations of its derivatives, with a total output of 20 channels or more. The derivatives could also be obtained by other coils overlaying the four shown here, so that the combinations take place before the SQUIDS, thereby increasing the number of SQUIDS. Either way, coils 1+2+3+4 yield B_z , 1+2-3-4 yields one "sideways" derivative, 1+3-2-4 yields another first derivative, etc. Some second derivatives are also possible. This system depends on lower-noise SQUIDS than are presently commercially available.

If we step back and remove ourselves from the trend of measuring the field normal to the scalp (B_z) at many locations in a big dewar, we can perhaps begin to look at the problem from a different perspective. We can consider two very different ideas as possible solutions. The first is to use only one dewar with a small tail diameter; the tail would here contain an array of coils designed to recognize B_z and its higher derivatives at various distances from the scalp, and essentially B_z at only one location. This is illustrated above in Fig. 2.

This system could use each MEG channel with a new effectiveness; it also uses the feature of the MEG, not possible with the EEG, where the detectors can be arrayed in a falloff line from the head. Although the idea of planar gradiometers has been mentioned from time-to-time, and we use simple versions at MIT, what is suggested here is to push higher-order derivative coils to their limit.

The second idea is to consider measuring the magnetic scalar potential, instead of B_z , the field component. Magnetic scalar potential measurements are not part of our technology and there are no devices meant to do this. Magnetic measuring technology has developed to measure the field only. Then, how does one measure the very small magnetic potential from the brain? We can here consider one method, shown in Fig. 3. The idea is to measure the magnetic potential in the same way as the electric potential. However, the magnetic wire shown in Fig. 3 should not "short out" the potential; therefore no flux should flow, and the detector would be a high impedance device. To accomplish this, the SQUID sensor puts an opposing current through a coil around the wire. There are obviously two problems. The first is how to couple the flux in the wire into a SQUID. Perhaps there is hope with a high-T superconductor, where a pick-up coil can be closer to the outside, and perhaps the wire can even link through it. The second is noise generated by high- μ wires, such as molypermalloy. In any case, isn't this scheme worth looking at? It solves the problem of measurement far from the scalp; the measurements are made here directly on the scalp, and many magnodes could be used, just as with EEG electrodes. The view of the brain sources would be different than with B_z ; we would again be seeing only the tangential sources, but in this case the signal would not fall off rapidly with distance from the scalp, and deeper sources could be seen, over a broader area.

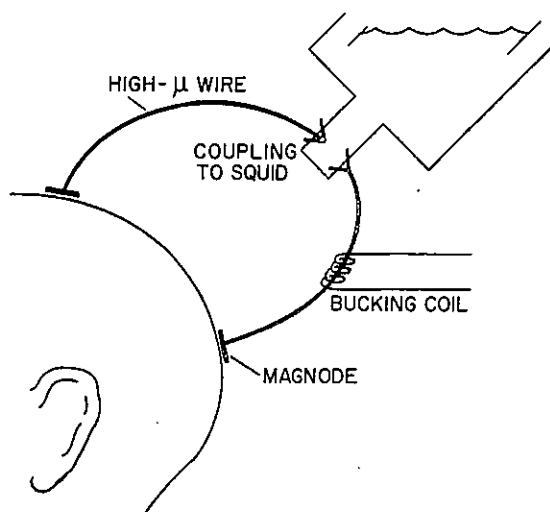


Fig. 3. A possible scheme for measuring the magnetic scalar potential of the brain. The high- μ magnodes and wire carry the magnetic potential to a SQUID device, which somehow senses the flux through the wire. To insure that the flux remains near zero (no "magnetic current"), a servo coil, powered by the SQUID, introduces an opposite flux in the wire. The current through the wire is then proportional to the magnetic scalar potential difference between the two magnodes.

It is hoped that the presentation of these two schemes will stimulate others to produce yet different schemes for solving the problems of biomagnetism.

FUTURE PROSPECTS

I have asked various colleagues in the U.S. where they thought biomagnetism is headed, and what the fruit will be. There was a range of answers, but all included the MEG as the main application for the future; the system will consist of large sensor arrays, probably using cryoSQUIDS, and perhaps high-T superconductors in some form. There were differences, however, in how we would get there. One cautious colleague said that before the applications in the brain were clear and solid, there would be much "slugging it out in order to show the definite advantages, probably by using both magnetic and potential techniques on the same subject". Another colleague feels that the MEG will be accepted more readily than that; he was recently quoted in a newspaper as saying, in regard to routine annual MEG brain check-ups, that "it's no longer a question as to whether such an annual MEG check will be developed - it's a question of when."

But I'd like the privilege of also giving my own thoughts here, and perhaps I speak for some of you as well. In measuring the magnetic fields of the body, even though we've made strong advances, I have a feeling that we are somehow missing a magic key which will unlock things. It is the feeling that some lucky person will come along one of these days with an idea, and say: "Hey, don't you see, when you combine this field component with this potential then things cancel out and you have all this new information!" In that case the future of biomagnetism will be something none can foresee at this time, and we cannot yet imagine what the fruit will be.

In any event, the many papers presented at this Tokyo conference will bring the future that much closer.

ACKNOWLEDGEMENT

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MAGNETOMETRY - A TOOL FOR STUDYING THE CELL BIOLOGY OF MACROPHAGES

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INTRODUCTION

Iron oxide particles serve as a non-toxic marker for studies in living cells and organs. They are easily recognized in living or fixed cells by light microscopy and by electron microscopy because of their electron density. Some forms of iron oxide can be magnetized. Then particle motions can be either measured or manipulated externally. Magnetic fields from particles ingested by mononuclear phagocytes (macrophages) in the lungs, liver, or skin can be measured with fluxgate or with SQUID (Superconducting Quantum Interference Device) magnetometers. This paper details how magnetic particles can be used to monitor phagocytosis, organelle motion, and cytoplasmic viscosity in normal and compromised cells.

RESULTS AND DISCUSSION

Phagocytosis. After magnetic particles are ingested by phagocytic cells we have found that, following magnetization, the remanent field exhibits decay. This decay is called relaxation (Cohen, 1973) and is caused by a progressive reorientation of particles away from their initially aligned state; the vector sum of the fields from individual particles decreases. Interestingly, relaxation in the lungs changes with time after exposure to particles (Brain et al., 1984a; Gehr et al., 1983c). Relaxation is initially slow, but later speeds up.

As shown in Figure 1, we have observed the same phenomenon in the skin after Syrian golden hamsters received an intradermal injection of magnetite (Brain et al.,

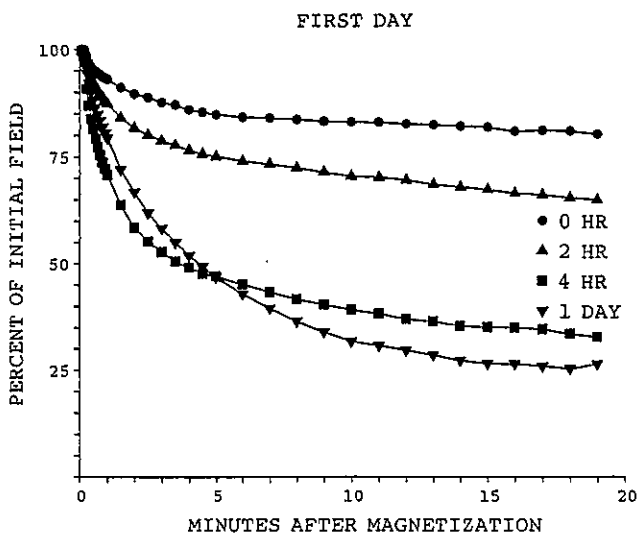


Fig. 1. Relaxation curves above the skin from 6 Syrian golden hamsters at 4 times after the intradermal injection of 0.05 mg Fe_3O_4 . The data are shown with the initial field strength (B_0) of each curve normalized to 100%.

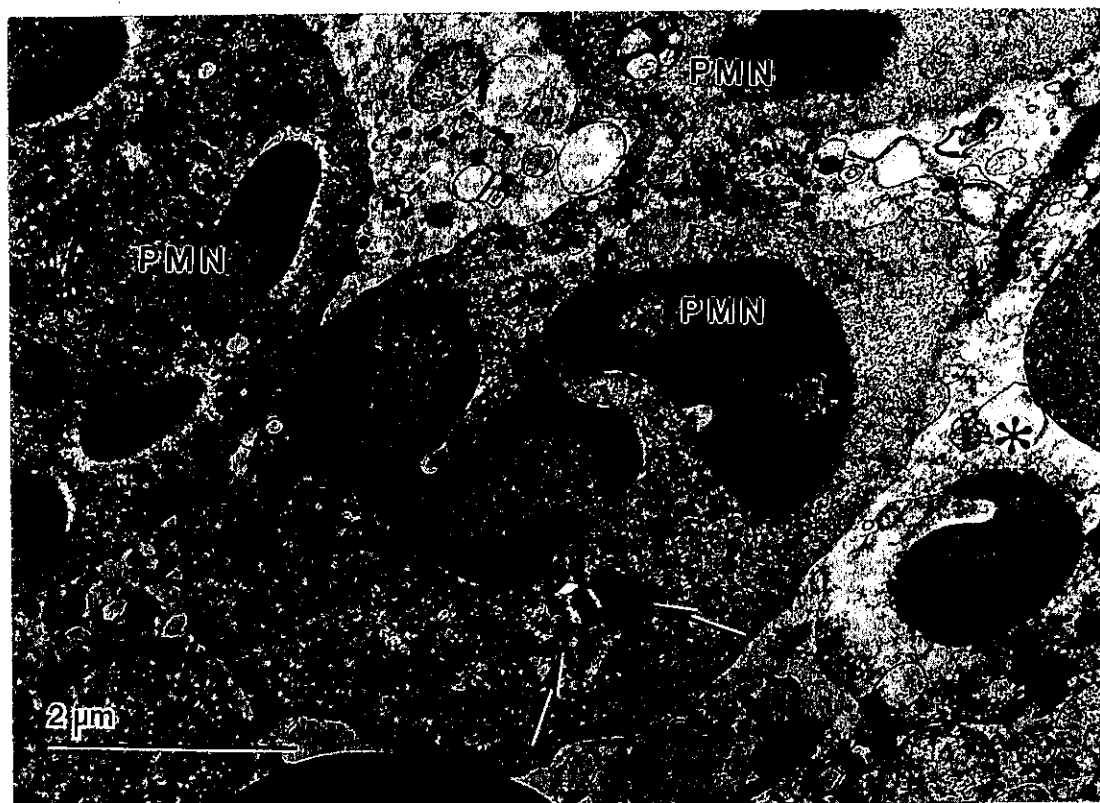


Fig. 2. A section of the papillary layer of the dermis in a hamster injected with Fe_3O_4 24 hours earlier viewed with the electron microscope. We found that a dense, mostly neutrophilic infiltrate formed at the injection site at this time. In the center of the micrograph above, one can see a mostly degranulated neutrophil which contains some magnetite in a phagosome (see arrows). To the right is a degenerated neutrophil (see star), another common finding.

1985a). Relaxation is very slow immediately after the particles are injected, but the rate increases dramatically with increasing time post-injection. After the first day, relaxation rates then remain stable for weeks. We believe that the early increase in relaxation rate seen in our data represents the transition from extracellular particles to phagocytized particles. Both lung and skin studies demonstrate that intracellular particles relax faster than free particles; therefore, non-invasive magnetometry can be used to follow the progression of *in situ* phagocytosis (Brain et al., 1984a).

Organelle Motion. What causes the ingested particles to change their alignment? Relaxation curves can be interpreted by considering the following factors. First, the phenomenon reflects physical movement (rotation) of the magnetic particles since the magnetization of individual particles doesn't decrease. Secondly, we must consider the forces available to move particles within phagocytic cells. Finally, we must consider the milieu in which the particles are found. The rheologic properties or physical consistency of the medium surrounding the particle-containing organelle will influence the effectiveness of the applied forces.

Our *in vivo* experiments as well as our ultrastructural studies suggest that the motions of phagocytized particles come largely from the actin-driven intracellular

movements of phagosomes and phagolysosomes that contain the particles (Brain et al., 1984a, 1984b; Gehr et al., 1983b, 1983c). While initial experiments focused on magnetic particles in macrophages in the lungs and liver, we now report similar ultrastructural results in dermal phagocytes. Our recent studies in hamster skin show that at 1 day (when relaxation is brisk; see Figure 1) the injected particles are almost exclusively intracellular (Brain et al., 1985a). Figure 2 shows some magnetic particles located within a neutrophil. At 1 day post-injection the majority of the injected magnetite particles are found within neutrophils. Thus, for the first time, we use magnetometry to demonstrate organelle motion in polymorphonuclear leukocytes. During the next week, the particles remain intracellular but are gradually transferred to macrophages in the same location. Relaxation remains constant showing that neutrophils and macrophages in the skin have similar organelle motion.

Thus in the lungs, liver, or skin we believe that magnetic particle movements (relaxation) arise from the motile elements of the cytoskeleton. These contractile intracellular proteins orchestrate the cell movements required for functions such as phagocytosis, organelle translocation, secretion, or amoeboid movement. Even in the motionless lung of a dead animal, relaxation continues as long as the alveolar macrophages are kept warm and oxygenated (Brain et al., 1984b).

The hypothesis that organelle motion is the dominant mechanism for relaxation has also been confirmed in studies of animal and human pulmonary macrophages observed *in vitro* (Gehr et al., 1983a; Valberg 1983, 1984; Valberg and Albertini 1985; Nemoto et al., 1985). Cultured macrophages containing magnetic particles exhibited relaxation that was similar to that seen *in vivo*, confirming that cardiac and respiratory movements are not essential for particle motions.

Cytoplasmic Viscosity. The rheologic properties of cytoplasm can be measured using magnetic particles and optical methods (Crick and Hughes 1950; Sato et al., 1984). Alternatively, magnetometry can be used instead of direct visualization (Valberg 1984, Valberg and Albertini 1985; Valberg and Butler, 1987). The forces resisting organelle movement are important to know since rates of phagocytosis, movement, and exocytosis in cells are influenced by cell viscosity. Previous investigators have generally used either very large particles (~100 μm) or molecular probes of small size (~0.003 μm). The larger particles were observed optically, and the molecules were monitored by techniques that essentially measure their diffusion mobility. In contrast, our magnetic particles are an intracellular probe which are comparable in size to cell organelles (~0.5 μm). As shown in Table I, the apparent viscosity is heavily dependent on the size of the probe. Small particles encounter low viscosity while large particles encounter much higher viscosities. We also use a nonoptical method that is easier to quantify for large numbers of cells. In our magnetometric method, particles are twisted while in one area of the cell. No translocation across intracytoplasmic barriers is required.

Fluids in which viscosity is a constant independent of shearing rate are known as Newtonian fluids. In contrast, fluids such as cytoplasm exhibit variable apparent viscosities at different shear rates and are called non-Newtonian fluids. For Newtonian viscosity, the angle through which a phagosome containing a magnetic particle would be twisted by a magnetic field depends on the product of the twisting field magnitude and the duration of its application. We have verified that magnetic particles behave in a predictable way when suspended in Newtonian fluids of high viscosity (Valberg and Butler, 1987). For non-Newtonian fluids, viscosity depends on shear rate (e.g., dilatant vs. pseudoplastic) or time (e.g., rheopectic vs. thixotropic). In cells, in addition to departures from Newtonian viscosity, impediments are presented to rotation by formed structures in the cytoplasm. However, it is still possible to estimate apparent visco elastic parameters for the particle environment.

For determination of the viscosity of the particle environment, particles are

TABLE I
Selected experimental measurements of cytoplasmic viscosity

Investigators, Date	Experimental Parameters				
	Cell System	Method	Particle Diameter [μm]	Shear Rate [s^{-1}]	Apparent Viscosity [$\text{Pa}\cdot\text{s}$]
Crick and Hughes, 1950 ^[1]	chick fibroblasts	magnetic dragging, optical analysis	2-5	1.4	~ 1
Mastro et al, 1984 ^[2]	Swiss 3T3 cells	ESR, PCAOL	0.0006	n.a.	0.002-0.003
Luby-Phelps et al, 1986 ^[3]	Swiss 3T3 cells	FPR, dextran	0.0012	n.a.	0.004
Wojcieszyn, et al, 1981 ^[4]	foreskin fibroblasts	FPR, BSA	0.0072	n.a.	0.08
Valberg and Albertini, 1985 ^[5]	pulmonary macrophages	magnetometry of twisted particles	0.3-0.7	0.001-0.003	1200-2700
Sato, et al, 1984 ^[6]	squid axoplasm	magnetic dragging, optical analysis	83-213	0.0001-0.004	$10^4 - 10^5$

Viscosity of $\text{H}_2\text{O} = 0.0007 \text{ Pa}\cdot\text{s}$ at 37°C .

BSA = bovine serum albumin; FPR = fluorescence photobleaching recovery; ESR = electron spin resonance; PCAOL = tetramethyl-methanopyrroline-N-oxyl; n.a. = not applicable, molecular diffusion does not have a defined shear rate.

[1] *Expt. Cell Res.* 1:37-80 (1950).

[2] *Proc. Natl. Acad. Sci.* 81:3414-3418 (1984).

[3] *J. Cell Biol.* 102:2015-2022 (1986).

[4] *Proc. Natl. Acad. Sci.* 78:4407-4410 (1981).

[5] *J. Cell Biol.* 101:130-140 (1985).

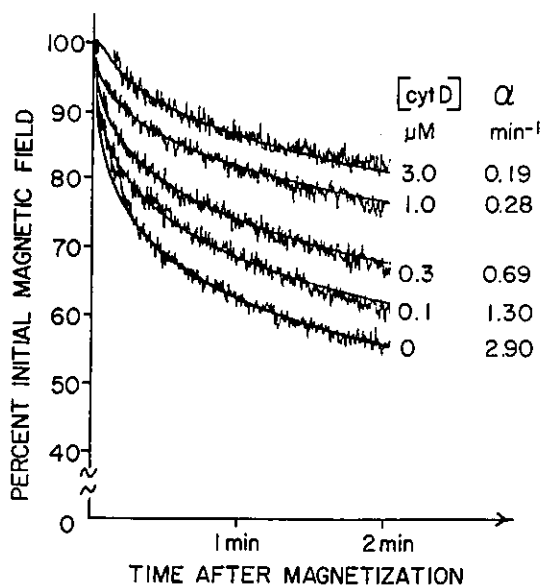
[6] *Cell Motility* 4:7-23 (1984).

initially magnetized with a strong magnetic field. Then, a weak magnetic field is applied perpendicular to the axis along which the particles were aligned by the initial magnetization. Thus, the particles can be made to exert a known force on their environment and thereby probe both resistance to movement and elastic recoil. For example, the rate at which the particles realign toward this "twisting" field is related inversely to the viscosity of the medium surrounding the particles.

We estimated that the cytoplasmic viscosity of oxygenated cells at 37°C ranges from 12,000 poise at shear rates of 0.03s^{-1} to 27,000 poise at shear rates of 0.001s^{-1} . The viscosity of H_2O at 37° is 0.007 poise. Interestingly, cooling, but not cytochalasin D, increases the viscosity of the cytoplasm of hamster pulmonary macrophages. These results suggest that whereas cooling the cytoplasm may both inhibit force generation and increase cytoplasmic viscosity, cytD primarily inhibits force generation and does not dramatically alter cytoplasmic viscosity. Elasticity could also be observed by applying the twisting field for one minute while monitoring the remanent field. The curves demonstrated yield followed by elastic recoil of the cytoplasm.

Magnetometric-Functional Correlates. We believe that magnetometric estimates of cell motility are related to other measures of cell motion such as particle ingestion. Hamster lung macrophages were incubated with albumin-coated latex particles in the presence of different Cytochalasin D (CytD) concentrations, a substance known to interfere with actin filament polymerization. Phagocytic function was assayed using flow cytometry and fluorescence microscopy to quantify the number of 2.4 μm diameter fluorescent particles ingested by individual cells. Five min CytD incubation inhibited latex bead ingestion by cells (50% @ 1 μM , 99% @ 10 μM) (Parod and Brain 1986). The ability of CytD to interfere with generation of cytoplasmic motion was then examined magnetometrically in macrophages which had previously ingested magnetic particles (see Figure 3). We found a strong correlation between the inhibition of organelle motion and the inhibition of particle ingestion by cells measured previously (Parod and Brain, 1986). As shown in Figure 4, the similarity of the two dose-response curves suggests that the same "motor" that moves intracellular organelles is necessary for the ingestion of particles from the cell surface into phagosomal vesicles.

Fig. 3. Relaxation in hamster lung macrophages recovered by lung lavage and studied *in vitro*. The concentration of cytochalasin D (cytD) has been varied between 0 and 3.0 micromolar (μM). The irregular lines are the experimental record of the relaxation curves obtained at the cytD concentrations shown. The corresponding solid lines are the curves with the best fit to the model having values of α as shown. This mathematical model is described in Valberg and Butler (1987).



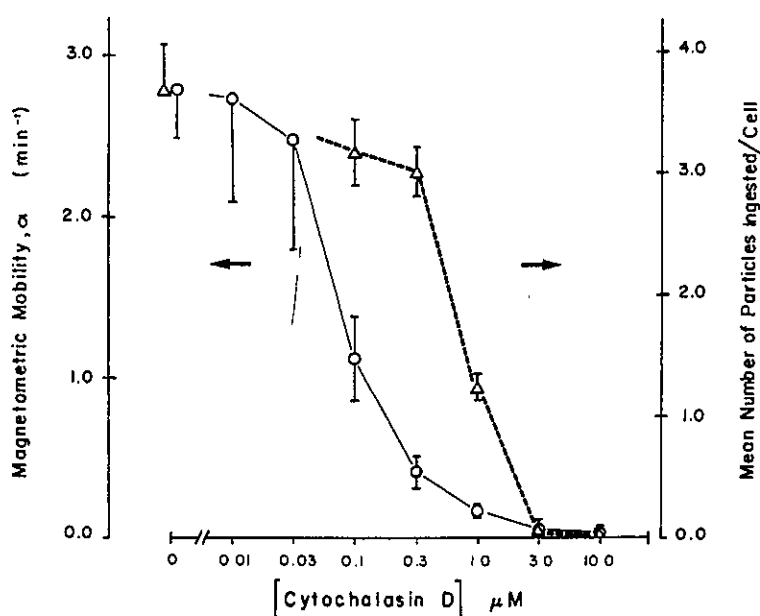


Fig. 4. The effects of cytochalasin D on magnetic mobility and particle ingestion by hamster lung macrophages are compared. Intracellular magnetic particle motion is parameterized by α (left axis), and the dependence of α on cytD concentration is given by the solid curve. Latex bead ingestion, expressed by the number of beads internalized (right axis), is shown by the dashed curve.

Many magnetometric-functional correlates exist *in vivo* as well. Perfluorochemical emulsions (PFC) are being used experimentally as blood substitutes in animals and man. However PFC is taken up by macrophages in the liver and may have adverse effects on them (Weinstock et al., 1986). As shown in Figure 5, in rats, we observed a dramatic slowing of relaxation beginning 1 hr after PFC injection. Importantly we found that PFC also altered the fate of bacteria in the blood (Molina et al., 1987). PFC caused decreased uptake of *Pseudomonas aeruginosa* by the liver and increased uptake by the spleen and lung. We also saw significant decreases in killing of *P. aeruginosa* in PFC animals when we compared the number of viable bacteria recovered from organ homogenates at 1 versus 4 hours. PFC also depressed the rate of *S. aureus* removal from the circulation. These functional changes in macrophages were correlated with changes in organelle motion detected by magnetometry.

CONCLUSION

In summary, we have shown that magnetometry can be used to non-invasively assess *in situ* particle phagocytosis as well as events reflecting cytoplasmic viscosity and cell motility. We will continue to evaluate, both *in vivo* and *in vitro*, the effects of various environmental and pathological conditions on cell function.

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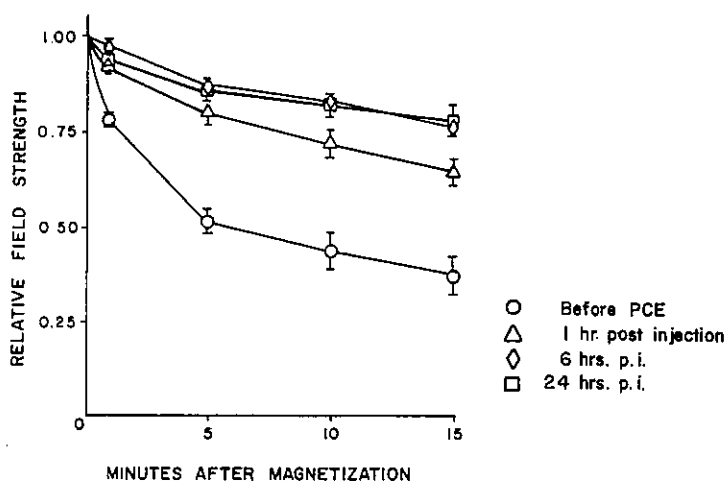


Fig. 5. The effects of artificial blood on the phagosomal motion of hepatic macrophages in Sprague-Dawley rats. Each animal was first injected intravenously with 1.5 mg/kg of submicrometric magnetic gamma-hematite. As described in Weinstock et al. (1986), several days later each rat was injected with 2.0 ml/100gm of PCE. PCE contains particles of F-DMA-F-nonane 12.55% v/v in water and pluronic F68 emulsifier, starch and electrolytes. As seen above, we observe a dramatic slowing of relaxation beginning 1 hr after PCE injection. Prior to PCE, the initial relaxation rate, λ , was 20.7%/min. At 1 hr post-PCE, λ had decreased to 9.0%/min and by 6 hrs λ was 3.3%/min. With time λ increased but remained lower than controls even at 30 days ($\lambda = 15.7\%/min$). When we examined tissue sections of the liver with an electron microscope we saw abundant vacuoles (nonane particles) in Kupffer cells.

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METHODS AND INSTRUMENTATION FOR BIOMAGNETISM

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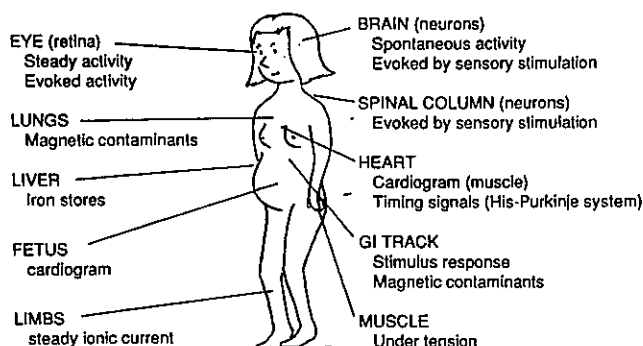
INTRODUCTION

Biomagnetism is the study of biological activity through analysis of the magnetic fields such activity produces. This paper is a brief explanation of the principles of biomagnetism, focussing on the instrumentation that make such studies possible and how these measurements are used to learn about the underlying biological structures and events that can be deduced from them. This is not meant to be a comprehensive review, and some important areas of study will not even be mentioned. Readers who wish a more complete coverage may consult a textbook which provides an extensive introduction to this broad topic (Williamson et al., 1983), the proceedings of the last international conference on biomagnetism (Weinberg et al., 1984), and a general review (Williamson and Kaufman, 1981).

BIOMAGNETIC FIELDS

Many organs of the human body produce magnetic fields, as depicted in Fig. 1. There are three classes of sources: magnetic materials, the magnetic susceptibility of tissue, and ionic electrical currents. The first biomagnetic field to be observed from magnetic materials was associated with particles lodged in the lungs, as well as other organs in the thorax (Cohen, 1975). More difficult to observe is the effect of tissue susceptibility, because its value is close to that of water, the body's major constituent, and its value is quite low (Farrell et al., 1978). Nevertheless for patients with substantial iron overloads in the liver, measurements of that organ's susceptibility *in vivo* provide a clinically important measure of the concentration of iron (Brittenham et al., 1982). The class of fields that has attracted the most interest are those arising from electrical currents in the body. The strongest field is associated with the strongest current, that of the heart muscle (Cohen, 1970). The earliest biomagnetic studies focused on mapping at various places across the chest the time-course of cardiac activity, called the *magnetocardiogram* (MCG). A related subject of prime interest is the conduction system of the heart, including the His bundle and Purkinje system that carry excitations from the pacemaker to the ventricles. While these rapidly-moving signals are difficult to observe, the clinical importance of developing a noninvasive technique to monitor the conduction system has encouraged intensive research (Erné, 1985). The greatest emphasis has been concentrated on much weaker signals from neural activity within the brain, or *magnetoencephalogram* (MEG). Studies of spontaneous and sensory-related brain activity have demonstrated

Fig. 1. Representative magnetic fields of the human body.



their importance for both basic and clinical research (For reviews see: Hari and Ilmoniemi, 1986; Romani and Narici, 1986; Williamson and Kaufman, 1987). Even the very weak fields associated with brainstem activity have been detected (Erné et al., 1987). Recently, magnetic fields have also been observed in the vicinity of the spinal cord in humans (Mizutani and Kuriki, 1986).

These kinds of studies have stimulated interest in better understanding the underlying physiology that gives rise to the fields. Thus Wikswo et al. (1980) studied the field associated with the action potential of an isolated nerve axon *in vitro* and demonstrated that the observed field is due to intracellular currents. Simultaneous measurements of both transmembrane potential and the magnetic field near a nerve have validated the underlying theory and provide accurate measurements for the conductivity of the intracellular medium (Roth and Wikswo, 1985). In a similar spirit, research has begun on isolated brain tissue to gain understanding of the underlying mechanisms when populations of neurons are active (Okada and Nicholson, 1987; Tesche et al., 1987).

INSTRUMENTATION

While studies of these types have secured for the biomagnetic approach an accepted place in a variety of specialized disciplines, work continues toward developing improved measuring techniques. All biomagnetic fields are extremely weak, the strongest being about 10^{-6} of the earth's steady field of 70×10^{-6} tesla (or 70 μ T). Thus the QRS peak of the cardiac field is typically 25×10^{-12} T (or 25 pT), the much weaker alpha rhythm of the brain is about 1×10^{-12} T (or 1 pT) and sensory-evoked fields are about 100×10^{-15} T (or 100 fT). In virtually all cases the investigator must cope with two problems: the weakness of the signal and the strength of competing magnetic noise in the environment. Here we discuss only the basic concepts of how to deal with these problems, for details can be found in a recent review (Romani et al., 1982a).

SQUID Sensors

A cryogenic instrument known as a *superconducting quantum interference device* (SQUID) is used for the most sensitive biomagnetic studies. It is conventionally maintained in a bath of liquid helium at a temperature of 4.2 K (or -269 C), isolated from the outside by a vacuum-insulated container known as a *dewar* whose external surfaces are at room temperature (Fig. 2). Two components of this system merit special attention: one is the SQUID itself and the other is a *detection coil* that is placed as close as possible to the field source. The detection coil is part of a closed-loop superconducting circuit, called a *flux transformer*, with the leads of the coil passing upward to enter the SQUID enclosure where they form a *signal coil*. One property of a closed superconducting loop is that if a magnetic field is applied anywhere within the loop, the superconducting electrons flow through the wire so that their current produces a field that maintains the net magnetic flux in the loop (product of field and area) invariant. Consequently, if a magnetic field passes through loops of the detection coil, current passes around the entire circuit, and the portion flowing in the signal coil imposes a field on the SQUID. Room temperature electronics monitor the response of the SQUID and provide a voltage that is proportional to the magnetic flux in the detection coil. The principal advantage of this arrangement is that the detection coil can be wound with a geometry best meeting the measurement

Fig. 2. Elements of a SQUID system for monitoring the magnetic field of a subject's brain.

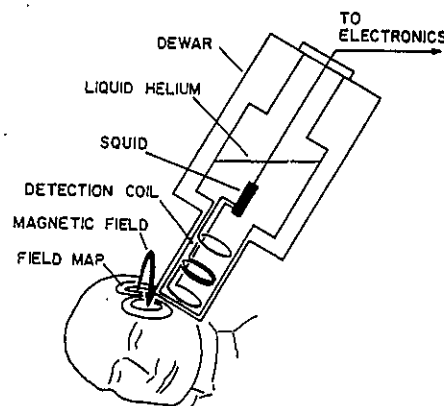
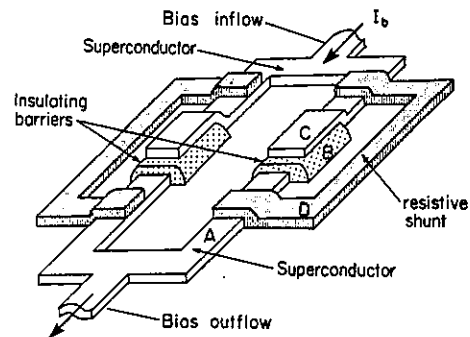


Fig. 3. A thin-film dc SQUID, with A and C being superconducting layers and B a thin insulator. Each junction has a parallel resistive shunt (D) for technical reasons, to avoid a hysteretic response when a magnetic field is applied.



requirements. For instance, Fig. 2 shows a coil having the geometry of a *second-order gradiometer*, namely, three equally-spaced coaxial coils with the center wound in the opposite sense and having twice as many turns as the end coils. This arrangement discriminates against fields from distant noise sources that are uniform in space, yet it retains sensitivity to fields from local sources that are appreciable only in the lowest coil (*pickup coil*). Thus the second-order gradiometer improves the signal-to-noise ratio. In less-noisy environments, such as a rural site or inside a magnetically shielded room, a first-order gradiometer may suffice. This has only two separated coils, wound in the opposite sense. In all gradiometers, the quality of noise rejection depends on how accurately the areas enclosed by each loop are made equal to each other. It is common to attach small pieces of superconducting foil at the appropriate positions to improve the area "balance" to 1 part in 10^4 or even 1 part in 10^5 . Detection coils of large diameter enhance sensitivity because they couple more signal energy. Typical diameters are 2 and 4 cm for studies of the brain and heart respectively.

With the advance of technology, thin-film techniques are becoming popular for fabricating SQUIDs. Figure 3 gives a simplified illustration of what is known as a *dc SQUID*. To operate this device a dc current that is fed into the superconducting film (C) at one end, divides and passes through two parallel arms, and recombines in the superconducting film (A) at the other end. Each arm is interrupted by a *Josephson junction*, which is simply a thin insulator (B) that breaks the superconducting circuit. This is named for Brian Josephson who developed the theory for the action of such an insulating junction between two superconductors. At low dc bias current, electrons can "tunnel" through the junctions without exhibiting resistance, but when the current is increased to an appropriate level both junctions exhibit a (common) voltage. This voltage is predicted by Josephson's equations and the electrical behavior of the circuit.

If a signal coil mounted above the area between the two arms applies a magnetic field, the voltage across the junctions varies periodically with increasing field. This arises from the fact that the field gives electrons passing along one arm a different momentum than electrons passing along the other, so there is an interference effect varying with field when the quantum-mechanical wave functions describing the two currents rejoin. The condition for periodicity is fixed by the value of the elementary *flux quantum* $\phi_0 = h/2e = 2 \times 10^{-15}$ tesla-meter², which is the smallest non-zero amount of flux that can exist within a closed loop of superconductor. Since the area within the arms of the SQUID is small, and the flux quantum itself is such a small value, counting voltage oscillations provides a sensitivity measure of how much the applied field has changed.

This device can be made to respond linearly with applied field, and the sensitivity can be enhanced by a factor of 10^5 or more by adding a feedback loop. With a second coil mounted over the area between the arms and appropriate electronic circuits to monitor the voltage across the junctions, a current can be fed to this coil so that its field just cancels the field of the input coil. With the SQUID serving as a null detector in this way, the voltage provided by the feedback current passing through a resistor is strictly proportional to the current of the signal coil, and hence to the biomagnetic field in the detection coil. The method provides excellent linearity in response, with a wide dynamic range. Other refinements are added to improve sensitivity, such as applying an ac rather than true dc bias, but it is not appropriate to go into such details here. Some commercial SQUID devices with detection coils of 2-cm diameter exhibit a sensitivity of about 20 fT within a 1 Hz bandwidth, and with careful optimization a sensitivity of 5 fT has been achieved. Emphasis has also been placed in developing multiple-sensor systems so that the process of mapping a field pattern over a portion of

the body to determine the underlying sources is greatly shortened (Ilmoniemi et al., 1984; Williamson et al., 1984; Romani et al., 1985; Knuutila et al., 1987). Since thin-film fabrication techniques offer many advantages for SQUIDS, there is interest in making detection coils in the same way. Indeed, with sufficient sensitivity, the use of higher-order planar gradiometers (as contrasted with the axial gradiometer shown in Fig. 2) may have advantages in localizing sources of biomagnetic signals.

Magnetic Shielding

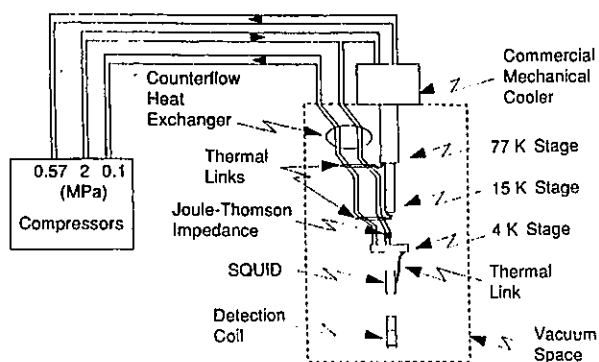
SQUID systems using a second-order gradiometer for the detection coil are capable of a wide range of useful measurements in an unshielded setting, including laboratories and clinics. However, ambient noise increases dramatically at low frequencies in noisy locations, and there may be additional noise at discrete frequencies from nearby machinery. High levels of radio frequency noise, as from communication systems, may also interfere with the operation of the SQUID. A room constructed with magnetic and radio-frequency shielding is one effective way to minimize these problems. The first rooms built for biomagnetic applications had four or more widely-spaced, concentric shells of high-permeability material (e.g., Mager, 1981) and are very effective. However, this requires a large space for installation, and the space inside is small, having a characteristic dimension of 2 m. Other magnetically shielded rooms have fewer shells, provide more working space, and yield acceptable shielding for most purposes (Kelh  et al., 1982; Buchanan et al., 1987).

SQUID Refrigeration

Everyone who uses a SQUID system recognizes that liquid helium as a coolant is a nuisance and considerable expense. There would be considerable advantage in using a refrigerator to cool and maintain the low temperature portions of the dewar. A SQUID requires very little refrigeration capacity, and the capacity to cool the electrical leads and insulating vacuum section is modest. The principal challenge is to limit the magnetic noise and vibration that such a system imposes on measurements. This was recognized by Zimmerman and Radebaugh (1978) who developed a successful closed-cycle cryogenic refrigerator, or *cryocooler*, based on a Sterling cycle. This has a long, motor-driven displacer that moves within a close-fitting sleeve to admit helium gas under pressure and subsequently achieve cooling by expansion of the gas as the displacer is withdrawn. It requires only 50 W of input power to produce temperatures of about 7 K, sufficient to operate a niobium rf SQUID that detected the magnetic field of the human heart.

Recently a different type of device has been developed with a noise level that is sufficient for measuring the magnetic field of the brain (Buchanan et al., 1987). It depends on both a commercial Gifford-McMahon refrigerator and a specially designed Joule-Thomson refrigerator, where high-pressure helium gas expands and cools as it passes through a small hole into a low-pressure region. The former cools the dewar from room temperature and maintains a 15 K stage, and the latter is suspended from this cold stage and produces a stable temperature of about 4 K. Figure 4 shows the arrangement of gas lines and thermal links, most of the latter fabricated of fine copper wire. Since there are no mechanical links to the dewar, only fine tubes for conducting helium gas, this device can be easily rotated to operated in nearly any orientation, including horizontally and almost upside down. This makes it especially attractive for measurements about the head. We call this device "CryoSQUID". Movement of the G-M displacer produces magnetic noise, but only at well-defined frequencies. In practice, the noise is so stable that obtaining an average of its time series for 15 seconds or so with a personal computer is sufficient to subsequently allow the computer to subtract this noise in real time

Fig. 4. Schematic for gas flow lines and thermal links in the CryoSQUID system.



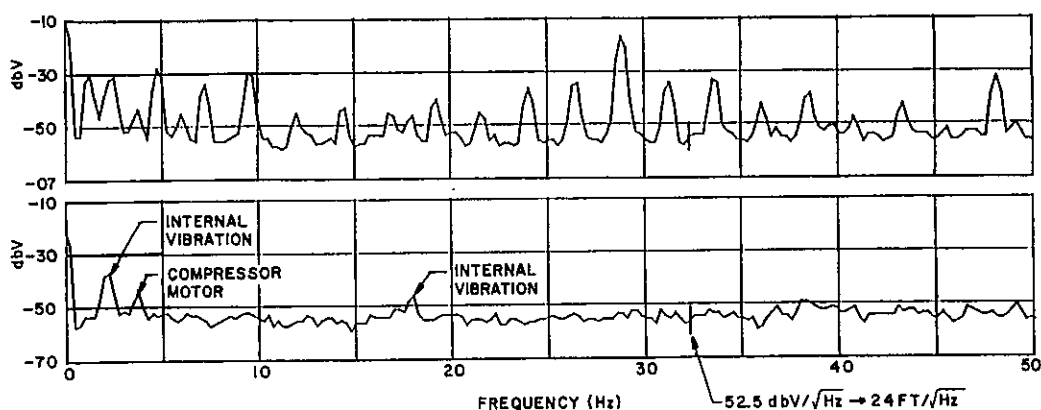


Fig. 5. Noise spectral density of CryoSQUID when the system operates without an adaptive filter (upper panel) and with it (lower panel).

from the incoming data. Figure 5 shows that virtually all of the refrigerator noise is eliminated. With this success it is clear that refrigerator-based SQUID systems are now feasible, eliminating the dependence on a steady supply of liquid helium.

PHENOMENA AND METHODS OF STUDY

Magnetic Particles

Magnetic particles exhibit a remanent field once a magnetic field of sufficient strength is applied and then removed. This remanent field is generally permanent, and so the presence of small quantities of magnetic materials can be detected with high-sensitivity sensors. In this way changes in the amount or distribution of particles can be inferred (Cohen, 1975). The technique has been applied to assessment of occupational health in environments where magnetic particles are inhaled (Kalliomäki et al., 1976; Freedman et al., 1980). It has also been exploited to provide evidence that smokers clear particles from their lungs more slowly than non-smokers (Cohen et al., 1979). More recently the study of the remanent field from the lungs of small animals where dust had been intentionally introduced into the lungs has revealed that time-dependent phenomena are caused by cellular activity. The steady decline of the remanent field outside the chest after application of a strong magnetizing field can be attributed to rotation of the particles that have been taken up by cells called "macrophages", which are - so to speak - the garbage trucks of the lung (Gehr et al., 1983a). Corresponding behavior has also been discovered within cells of the liver (Gehr et al., 1983b). Thus, studies of this type are revealing aspects of cell physiology that cannot be obtained noninvasively by other techniques (Nemoto, et al. 1985). Measurements of this kind can be carried out by a device called a fluxgate magnetometer, which requires no cooling.

Ionic Currents

Application of biomagnetic techniques to studies of organs such as the heart and brain are motivated by several factors. One is the fact that a magnetic measurement represents a different kind of spatial weighting of the source currents than electrical measurements across the skin, thus suggesting that different kinds of information will be obtained (Wikswa, 1983). Another is the possibility that the nature of intervening tissue may be less important in influencing the field pattern than the potential pattern across the skin. The overriding advantage of magnetic measurements in our opinion is the possibility of determining more accurately the location of confined regions of activity, when the activity can be modeled as a *current dipole*, namely, a small element of current. Localization provides a means of relating observed activity to specific regions of the body, such as in establishing functional maps of the brain. One example is discovery of a tonotopic organization across the auditory cortex of human subjects (Romani et al., 1982b) or in defining the region of an infarct in a diseased heart (Saarinen et al., 1985; Gonnelli et al., 1985).

Locating a Source

If the source is a current dipole, there will be one region where the field is strongest emerging from the body and another region where it is strongest entering the body. For a body with certain types of symmetry, such as one which can be approximated by a flat surface covering a semi-infinite, uniform conducting region (the *half-space model*), the source lies midway between these field extrema and at a depth that is equal to the distance between the extrema divided by $\sqrt{2}$ (≈ 1.4). Similarly, for a current dipole in a sphere, the depth of the source can be deduced from the ratio of the distance between the extrema to the radius of the sphere (Williamson and Kaufman, 1982). Such simple recipes, which are useful for making first estimates, can be refined by more accurate numerical models describing the appropriate region of the body.

There are cases where the field patterns from two or even three simultaneously active sources have been analyzed to reveal the positions of underlying activity; but in general the problem of dealing with multiple sources is just in its infancy. Much more theoretical and experimental work is needed to deal with the more interesting problems of the time sequence of multiply active areas in the brain or the interplay of Purkinje system and myocardium in activating the heart. In all these cases it should be kept in mind that there is no unique solution for the configuration of electrical sources that can be deduced from electrical potential measurements, or magnetic field measurements, or a combination of the two. Electrically and magnetically "silent" sources exist, in the sense that there are source configurations that produce no skin potential distribution or external fields. Roughly speaking, skin potentials and magnetic fields provide complementary information, and there are cases where the two should be used together (Wood et al., 1985).

FUTURE PROSPECTS

Software Reduction of Noise

Biomagnetic measurements continue to face the problem of environmental magnetic noise when applied to the weakest signals. Most magnetically shielded rooms do not completely shield noise at very low frequencies, say below 1 Hz. With growing popularity in the use of systems with multiple SQUID sensors, it becomes feasible to dedicate one or more of the sensors to monitor the ambient noise as a *reference* for purposes of subtracting a portion of it from the noisy signal. Simple fixed electronic balancing techniques have already been applied with success for unshielded measurements (Williamson et al., 1984). We report here a new computer-based approach that in many practical applications markedly reduces excess low frequency noise. The references consist of three SQUID sensors oriented to monitor three mutually perpendicular components of the ambient field. The technique uses computer-controlled attenuators to adjust the amplitude of each reference that is subtracted from each of the signals so as to remove the correlated portion of the noise. Figure 7 gives an example of the kind of improvement that can be obtained within a magnetically shielded room. With such electronic noise cancellation, the noise level is essentially the intrinsic sensor noise from high frequencies down to a frequency below 0.1 Hz. This is sufficient to operate the SQUID sensors in a dc-coupled mode to monitor very low-frequency activity.

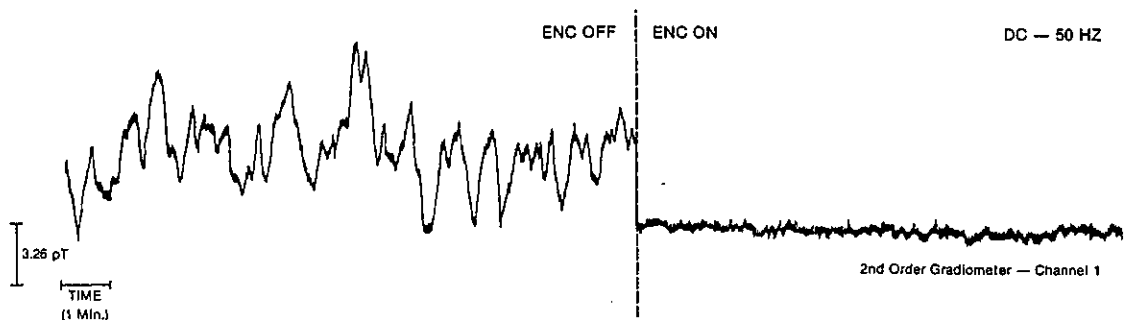


Fig. 7. Time course of the noise in the bandwidth DC-50 Hz observed within the magnetically shielded room at the Center for Neuromagnetism at Bellevue Hospital of the New York University Medical Center, without electronic noise cancellation (left) and with it (right).

High Temperature Superconductors

This past year marked a turning point in the development of superconducting devices with the discovery of superconductivity in the Yttrium-Barium-Copper-Oxygen ceramic system at temperatures as high as 94 K. The race is underway to find ways to make these materials practical for wires, thin films, and SQUIDs. One group recently reported success in making SQUIDs (Zimmerman et al., 1987) that operate up to 80 K. This clearly demonstrates that SQUIDs can be operated at liquid nitrogen temperatures (77 K), but unfortunately the noise levels are several orders of magnitude greater than those of the best SQUIDs operating in liquid helium. Whether high-temperature SQUIDs become useful for biomagnetic applications remains to be seen. Nevertheless, there is reasonable hope that high-temperature detection coils can be fabricated, and this would greatly ease the cryogenic problem. Dewars can be made thinner near the scalp, with a coil operating at 60 or 70 K, and since superconductors are poor conductors of heat the SQUID would not suffer. The prospect for applications of room-temperature superconductors is exciting indeed! When we think of arrays of sensors to measure the field pattern over a large area over the thorax or head, the chief advantage comes from being free from the constraints of a rigid dewar. Then the detection coil positions can be adjusted easily to match the contours of the particular individual. This will enhance signal strengths and permit convenient measurements for children and adults alike.

ACKNOWLEDGEMENTS

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SOURCES OF BIOMAGNETIC FIELDS

T KATILA

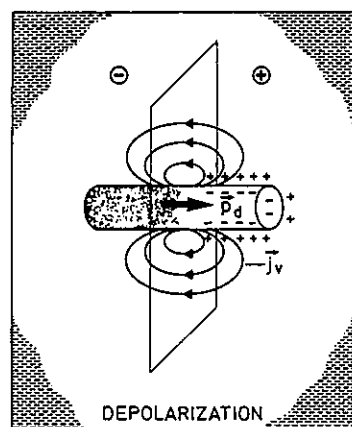
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1. BIOLOGICAL CURRENT SOURCES AT THE CELLULAR LEVEL

In the following, we will first consider a few examples of biological current sources at the cellular level. A living cell maintains a potential difference between the inside and the outside of the cell. In a static situation, most cells are electrically and magnetically silent. Excitable cells can produce electric surface potentials and external magnetic fields, which can be detected from outside.

In the human heart, one can find specialized cells for pacing, (sinus and atrioventricular nodes), for conducting the excitation (His Bundle with branches and Purkinje fibers), and finally muscle cells for mechanical work.

Fig. 1. The depolarization of a single muscle cell of the human heart (schematically). The primary current density is presented by a source current dipole $\vec{p}_d$. The figure also shows the associated volume current density $\vec{j}_v$ and the polarization of the cell membrane ($\pm$ signs).



We next consider the depolarization and the repolarization of a muscle cell in more detail (Fig. 1). The activation of a ventricular muscle cell could be described by utilizing modified Hodgkin-Huxley equations to account for measured data. Knowing the electric properties of the various parts of the cell and the surrounding volume conductor, the electric potential ϕ can be calculated. The volumes inside and outside the cell can, in the first approximation, be electrically modeled as passive, homogeneous, isotropic and ohmic volume conductors, although with different electric conductivities. Ohmic currents can be expressed as a gradient of the electric potential: $\vec{j}_v = -\sigma \nabla \phi_v$. Volume currents in a homogeneous volume conductor are ohmic and do not contribute to the magnetic field $\vec{B}_v = \nabla \times \vec{A}_v$. The label v refers to the volume conductor; the corresponding magnetic vector potential is $\vec{A}_v$.

Thus the magnetic field actually originates from the boundaries of the electric conductivity, and from the transmembrane current density of the cell, often called the *impressed current density*. We cannot repeat the calculation here, but it can be shown that the transmembrane current densities together with the axial current density inside the cell as a *primary current density* are approximately equal to the depolarization vector $\vec{p}_d$ shown in Fig. 1. The primary current dipole $\vec{p}_d$ is the *equivalent* source both of the electric potential ϕ_p and the magnetic field $\vec{B}_p$ in the extracellular volume conductor. It is the cylindrical shape of the cell

and the high electric resistivity of the cell membrane, together with its very specific nonlinear time dependent ionic conductivity, which give rise to the intracellular primary current source.

In a homogeneous and isotropic volume conductor, the electric potential produced by the current dipole $\vec{p}_d$ is,

$$\phi_{p,\infty}(\vec{r}) = \frac{1}{4\pi\sigma} \frac{\vec{p}_d \cdot \vec{r}}{r^3} \quad (1)$$

where $\vec{r}$ is the distance from the current dipole to the observation point. The subscript (∞) is to remind us that this potential is observed inside an infinite volume conductor. As indicated in Fig. 1, the zero potential is observed in a plane perpendicular to the dipole and crossing it. The corresponding magnetic field inside the volume conductor is,

$$\vec{B}_{p,\infty}(\vec{r}) = \frac{\mu_0}{4\pi} \frac{\vec{p}_d \times \vec{r}}{r^3} \quad (2)$$

Thus the spatial distributions of the magnitudes of the electric potential ϕ_p and the magnetic field $\vec{B}_p$ are similar, as long as they are rotated 90° relative to each other. In addition, their ratio reveals the conductivity σ of the volume conductor.

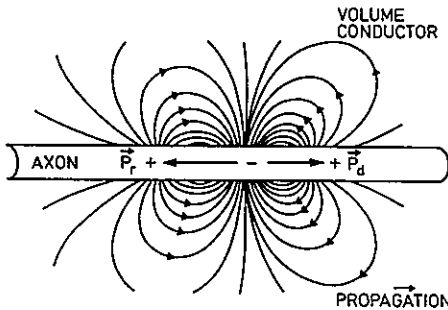


Fig. 2. A schematic presentation of the current sources of the action potential propagation in a single nerve axon. The current dipoles $\vec{p}_d$ and $\vec{p}_r$ can be associated with depolarization and repolarization phenomena, respectively.

The magnitude and the location of the depolarization vector $\vec{p}_d$ change with time. For the present purpose, however, we assume that the fields can be calculated in a quasistatic approximation. This means that the time dependences of the Maxwell's equations are neglected and they appear in calculating the extracellular potential and fields in the simple forms:

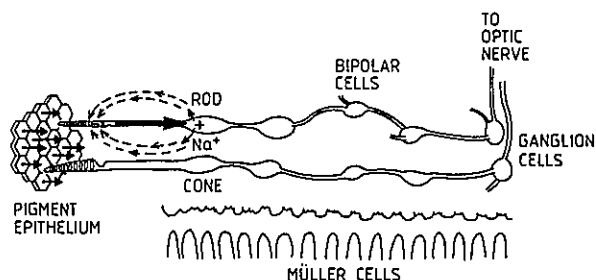
$$\nabla \cdot \vec{E} = \frac{\rho}{\epsilon_0}, \quad (3) \quad \nabla \cdot \vec{B} = 0 \quad (4),$$

$$\nabla \times \vec{E} = 0, \quad (5) \quad \text{and} \quad \nabla \times \vec{B} = \mu_0(\vec{j} + \nabla \times \vec{M}). \quad (6)$$

As a second example we consider a neuron with a single axon in an infinite, homogeneous volume conductor. An analytic solution of the action potential can be found in textbooks (see e.g. Ref. 1) but its derivation is beyond the scope of this article. Assuming that the repolarization takes place soon after the depolarization, the primary current sources of the action potential propagating in the axon can often be modeled with two closely spaced current dipoles, pointing in opposite directions (Fig. 2). The current dipole sources move along with the propagation of the action potential. Although this approach to the current source clearly is again an oversimplification, the magnetic field measured inside the volume conductor agrees reasonable well with the model [2]. In this case as well, the calculation of the magnetic field could be based on the measured electric potential. The potential solution stays essentially constant in shape but it moves along the propagation direction. Such a solution is called a soliton.

As one more example, let us consider bioelectric current sources in the neurosensory retina of the human eye. Current density is generated e.g. by pigment epithelium, photoreceptors and Müller cells. In Fig. 3, the transepithelium current density is depicted by arrows. The intracellular current density of a photoreceptor rod is shown by the large size arrow and the corresponding extracellular volume current density by broken lines. The source of the extracellular current density is at the base of the rod and the sink at the outer segment.

Fig. 3. Part of the neurosensory retina of the human eye. Current sources in the pigment epithelium and in a photodetector rod are shown by arrows. There are other retinal current sources, not shown in the figure.



Note that the current sources shown in Fig. 3 produce external potentials and magnetic fields also in the steady state. The photodetector rod can be excited via light input. This results in time dependent changes in the primary current sources and the corresponding fields. However, as long as the eye does not move, the positions of the sources stay essentially constant.

There exist a number of other sources of bioelectric and biomagnetic fields. As seen in Eq. (6), the magnetization of the biological material is one cause of biomagnetic fields. All biomaterial shows magnetization in an external magnetic field. Contaminating particles in the inhaled air, remaining in the lung, can show exceptionally strong magnetization phenomena.

2. DISTRIBUTIONS OF ELEMENTARY SOURCES

Assuming that the length of the depolarization phase in a single medial giant axon of a crayfish is $\Delta z = 3$ mm, and the intracellular axial current $I_z = 1 \mu\text{A}$, the value of the depolarization current dipole is 3 nAm. Ampère's circuital law can be used at radial distances below Δz to estimate the tangential component of the magnetic field. At a distance of 2 mm from the axis, the maximum field is about 100 pT. At a distance of 2 cm the field in the dipole field approximation decreases to about 1 pT. Due to the quadrupolar nature of the source (Fig. 2) the measured field value is considerably smaller /2/. Even with the most sensitive instrumentation presently available, the real time signal of a single giant axon becomes buried in the noise, when the measurement distance is of the order of centimeters.

From studies of the retinal bioelectric current sources /3/ the dipole moment of a single photoreceptor rod can be estimated to be around 10^{-16} Am. At a distance of 2 cm the smallest detectable current dipole within a bandwidth of 10 Hz is ~ 0.1 nAm. Thus about a million photosensory rods are required to give rise to a detectable signal in biomagnetic measurements. Cortical postsynaptic potentials could, as current sources, be of the order of 10^{-14} Am, but then a wider frequency band must also be used in measurements.

Thus in conventional biomagnetic studies, the signals measured are generally caused by a very large number of elementary current sources. When these sources are approximated by current dipoles $\vec{p}_{d,i}$, located at $\vec{r}_i$, the resulting fields within the homogeneous volume conductor can be calculated assuming that the superposition principle is valid. The magnetic field can then be expressed as:

$$\vec{B}_\infty(\vec{r}) = \frac{\mu_0}{4\pi} \sum_i \frac{\vec{p}_{d,i} \times (\vec{r} - \vec{r}_i)}{|\vec{r} - \vec{r}_i|^3} \quad (7)$$

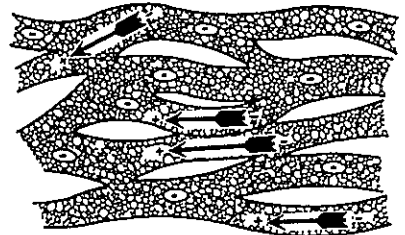
However, when the number of elementary sources is large, it is often more useful to define a (quasi-continuous) primary current distribution $\vec{j}_p$. For instance, the magnetic vector potential $\vec{A}(\vec{r})$ produced by the primary source currents could then be expressed as an integral,

$$\vec{A}_\infty(\vec{r}) = \frac{\mu_0}{4\pi} \int_{v'} \frac{\vec{j}_p(\vec{r}')}{|\vec{r} - \vec{r}'|} dv', \quad (8)$$

where we have assigned the infinitesimal current dipole element $d\vec{p} = \vec{j}_p dv'$. The symbol (∞) in Eqs. (7) and (8) again refers to an infinite and homogeneous volume conductor.

In the cardiac muscle, the muscle cells are joined together via special joints, as shown in Fig. 4. The spreading of the depolarization front is unisotropic and very complicated at the microscopic scale. This excitation front moves in normal cardiac muscle until the whole atrial or ventricular muscle is depolarized.

Fig. 4. In actual muscle cells, the depolarization appears as a front of elementary current dipoles, represented by the arrows. The volume currents are not shown.

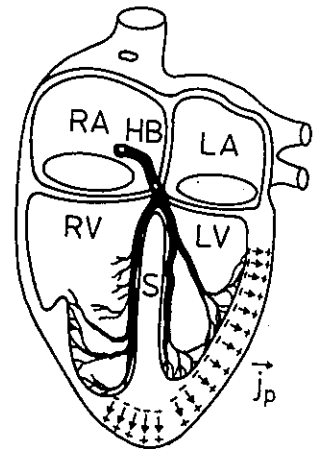


It was pointed out in Ref. /4/ that the interpretation of Eq. (8) is simplified if the primary sources $\vec{j}_p$ are confined to a subspace v' , whose dimensions are small when compared to the distance between the origin chosen (0) and the measurement point ($\vec{r}$). Then we can expand Eq. (8) to obtain a series of *equivalent* sources. The lowest order equivalent generator is the *current dipole* (see Figs. 6 a - c):

$$\vec{p} = \int_{v'} \vec{j}_p(\vec{r}') dv'. \quad (9)$$

The current dipole is thus the result of the simple vector summation of the primary currents.

Fig. 5. A cross section of the human heart. Parts involved in electric excitation of the heart are shown schematically. The cavities of the heart are: the right (RA) and the left (LA) atria, the right (RV) and the left (LV) ventricles, and the septum (S). The His bundle (HB), left and right bundle branches and the Purkinje network are also shown.



At times even before biomagnetic studies were made, the current dipole source had been used as an equivalent generator in bioelectric studies. Therefore, it was a natural choice as the first order generator in biomagnetic studies as well. However, several early reports on biomagnetic measurements used the *magnetic dipole* source as the basic equivalent generator. Indeed, it is shown in textbooks on classical electromagnetic theory, that the magnetic dipole is the lowest order nonzero generator, when the measurements are made outside the sphere containing all electric currents. In deriving this result, it is further assumed that the origin (source location) is at the centre of this sphere.

It was shown in Ref /4/ that if the source current distribution is confined to a subspace v' in a homogeneous volume conductor, the second order equivalent generators (Figs. 6d - h) include the three components m_x , m_y and m_z of the magnetic dipole moment vector $\vec{m}$. Thus the current multipole theory explains the roles of both the current dipole and the magnetic dipole as sources of biomagnetic fields.

Fig. 6. Equivalent source generators: p_x , p_y and p_z are components of the current dipole source vector $\vec{p}$. The current quadrupole generators are chosen in such a way that they include the components m_x , m_y and m_z of the magnetic dipole moment vector $\vec{m}$, and in addition two more generators. There are altogether nine second order generators, but only five of them are shown in the figure.

The second order generators or *current quadrupoles* are components of the following a - tensor:

$$a = \int_{v'} \vec{r}' \vec{j}_p(\vec{r}') dv'. \quad (10)$$

The generators in Figs. 6d - f present cases, where the primary (non-ohmic) currents are circular. They are components of the *magnetic dipole moment vector* $\vec{m}$,

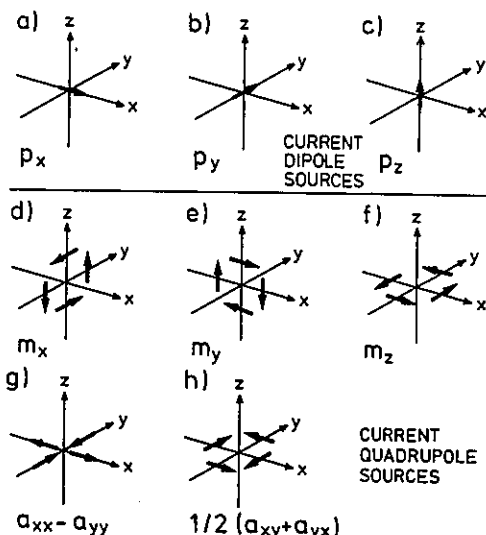
$$\vec{m} = \frac{1}{2} \int_{v'} \vec{r}' \times \vec{j}_p(\vec{r}') dv'. \quad (11)$$

While all components of the current dipole source contribute to the volume currents, the generators in Figs. 6d - f do not. Thus the latter generators are electrically silent and could be detected by magnetic measurements only. Other useful source models are e.g. the multiple dipole model and the double-layer model (see e.g. Ref. /5/).

3. THE INFLUENCE OF CONDUCTIVITY BOUNDARIES

We consider next the influence of conductivity boundaries on the measured potentials and fields. The electric conductivities of e.g. the human torso or the head are very complicated. To deal with such complicated structures, it is customary to assume that the volume conductor is piecewise homogeneous. In the following, we shall show that the inhomogeneities can be taken into account by introducing the so called *secondary sources* at the conductivity boundaries.

In the homogeneous and isotropic volume conductors the volume current density flows symmetrically, as shown in Fig. 7b. In Fig. 7a we assume that a plane boundary is placed close to the current source. We further assume that the electric conductivity is zero above the plane boundary. Hence no volume current density can flow across or above this plane. As a result, the volume current density flows asymmetrically, as in Fig. 7a. Fig. 7 also demonstrates that the current density in Fig. 7a is obtained as a sum of two kinds of current sources in a *homogeneous* volume conductor: the primary sources $\vec{j}_p$ (Fig. 7b) and the secondary sources $\vec{j}_s$ (Fig. 7c). The secondary sources are located at the conductivity boundary and their direction is perpendicular to it.



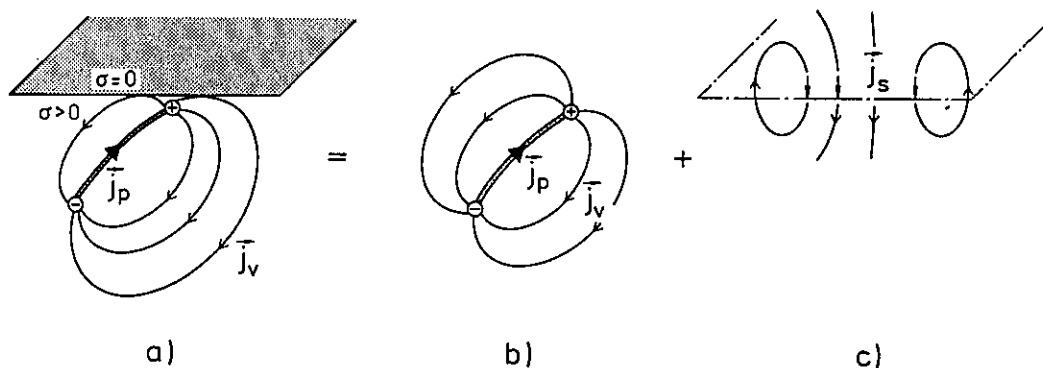


Fig. 7. a) In the presence of an electric conductivity boundary the volume current density becomes asymmetric. The resulting current distribution can be expressed as a sum of the following three current contributions: b) the primary source current $\vec{j}_p$ with its volume current density $\vec{j}_v$ and c) the secondary currents $\vec{j}_s$ with the associated volume current density.

Since the total current density is the sum of the primary and secondary contributions, we also can write the electric potential in the bounded conductor, ϕ_v , as a sum of the corresponding two terms,

$$\phi_v = \phi_\infty + \phi_s \quad (12)$$

and the corresponding magnetic field as,

$$\vec{B}_v = \vec{B}_\infty + \vec{B}_s. \quad (13)$$

In Eqs. (12) and (13), the first terms on the right side are due to the primary sources and second terms due to the hypothetical secondary sources. The principle of Eqs. (12) and (13) was stated by Helmholtz as early as 1853 /6/ and reformulated mathematically by Geselowitz /7/.

The task is to find the (hypothetical) potential double layer (or surface current distribution) which prevents the electric currents from flowing through the boundary, even though the electric properties of the volume conductor are identical on both sides of it. It turns out that such a secondary current density can be expressed as,

$$\vec{j}_s dv' = \phi_s \Delta\sigma d\vec{S} \quad (14)$$

where $d\vec{S}$ is a surface element vector, perpendicular to the boundary and $\Delta\sigma$ the difference of electric conductivities on the opposite sides of the boundary. The electric potential in the bounded volume conductor can be obtained from:

$$\phi(\vec{r}) = \frac{1}{4\pi\sigma} \int_v \frac{\vec{j}_p(\vec{r}') \cdot (\vec{r} - \vec{r}')}{|\vec{r} - \vec{r}'|^3} dv' + \frac{1}{4\pi\sigma} \int_s \phi_s \Delta\sigma \frac{d\vec{S} \cdot (\vec{r} - \vec{r}')}{|\vec{r} - \vec{r}'|^3}. \quad (15)$$

Note that Eq. (15) contains potential variables on both sides. In general, the equation must therefore be solved iteratively. When the potential on the left side is solved on surface S, further consideration of σ is needed.

Knowing now both the primary source currents $\vec{j}_p$, and the secondary sources $\vec{j}_s$ of the biomagnetic fields $\vec{B}$, the field becomes,

$$\vec{B}(\vec{r}) = \frac{\mu_0}{4\pi} \int_v \frac{\vec{j}_p(\vec{r}') \times (\vec{r} - \vec{r}')}{|\vec{r} - \vec{r}'|^3} dv' + \frac{\mu_0}{4\pi} \int_s \phi_s \Delta\sigma \frac{d\vec{S} \times (\vec{r} - \vec{r}')}{|\vec{r} - \vec{r}'|^3}. \quad (16)$$

This is the basic equation for calculating the biomagnetic field caused by an arbitrary current source distribution $\vec{j}_p$ in the approximation of a piecewise homogeneous volume conductor. Eqs. (15) and (16) can easily be extended to cases where there are several piecewise homogeneous subvolumes.

4. SOLUTIONS FOR BOUNDED VOLUME CONDUCTORS

Analytic solutions. In principle, the expressions above allow us to calculate the electric surface potential ϕ_s and the external magnetic field $\vec{B}$ caused by a given source current field distribution. However, analytic solutions are feasible only on some simple geometries of volume conductors, such as an electrically homogeneous and isotropic sphere. Since the current dipole in a homogeneous sphere is an important model case, we shall consider it in some detail. In Fig. 8, the current dipole is placed on the z-axis at a distance a from the centre of the sphere (Fig. 8 a). The electric surface potential ϕ_s for a radial current dipole is depicted in Fig. 8 b. The external magnetic field vanishes in this case identically.

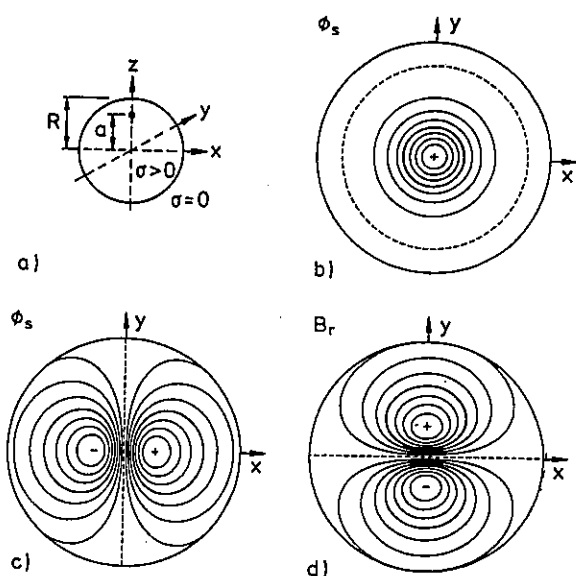


Fig. 8. Electric surface potentials ϕ_s (b and c) and the radial component B_r of the surface magnetic field d) produced by a single radial current dipole source b) and by a tangential current dipole (c and d). The insert a) depicts the position of the current dipole. The electric conductivity inside the sphere is assumed to be isotropic and homogeneous. The + and - signs indicate the potential and field extremes, the broken line shows the zero value. All maxima have been normalized to the same value.

The electric surface potential and the radial component of the magnetic field for a tangential current dipole $\vec{p}_x$ are shown in Figs. 8c and 8d, correspondingly, in a case where $f = a/R = 0.7$. The analytic expression of the surface potential is:

$$\phi_s(R, \theta, \varphi) = \frac{p_x \sin \theta \cos \varphi}{4\pi \sigma f R^2 \sin^2 \theta} \left(\frac{f^3 - 3f^2 \cos \theta + 3f - \cos \theta}{(1 - 2f \cos \theta + f^2)^{3/2}} + \cos \theta \right). \quad (17)$$

For a radial dipole, replace $p_x \sin \theta \cos \varphi$ by $p_z \cos \theta$. The radial component of the magnetic field is, when the source dipole is tangential:

$$B_r = \frac{\mu_0 p_x}{4\pi} \sin \varphi \frac{a \sin \theta}{|\vec{r} - \vec{a}|^3}. \quad (18)$$

Here, R is the radius of the sphere, φ and θ are angles defined the conventional way in spherical coordinates. When f approaches 1, the field patterns resemble those obtained for a tangential current dipole below a plane boundary.

It is interesting to compare the field patterns obtained from electric and magnetic measurements:

* Radial current sources produce non-zero electric surface potentials but zero external magnetic fields.

- * Tangential current dipoles produce both electric surface potentials and external magnetic fields.
- * For superficial tangential dipoles, the ϕ_s and the B_r show similar dipolar field patterns, but rotated by 90° relative to each other.
- * Deep dipole sources in a sphere can produce electric surface potentials but the magnetic fields become exceedingly small for sources close to the centre.

The last statement can also be derived from the fact that all dipole sources, located centrally in a sphere, are also radial.

Computational methods. In considering e.g. the realistic excitation front of the human heart and the torso as a volume conductor, only computer methods can handle the complicated primary and secondary sources of the problem (Ref. /8/). The computational techniques allow, in addition, a possibility to follow the time dependence of the bioelectric activation cycle more realistically. Thousands of source current dipole elements may be used for this purpose. Cardiac abnormalities, such as ischemia and infarction can be simulated by modifying the transmembrane action potentials in the appropriate region. Quite recently, the electric anisotropy of the cardiac muscle has also been taken into account. In brain studies, models imitating the electric flow of information at the cellular level and suitable for calculation of bioelectromagnetic fields are not yet available. Most often, a current dipole or multiple current dipoles are used as equivalent sources. Volume conductor models of the head, comparable to the torso models have been developed recently /9/.

6. CONCLUSION

We have discussed sources of biomagnetic fields at the cellular level and how various distributions of elementary current sources can be described by equivalent sources. The influence of electric conductivity boundaries was considered and examples of biomagnetic fields produced by equivalent current sources in bounded volume conductors were presented.

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